

DETAILED ACTION

Response to Amendment

1. Claims 39 and 40 have been amended and claim 49 has been canceled in the amendments filed November 23, 2011 and November 28, 2011. Following the amendments, claims 39-43, 45-48 and 52-55 are pending in the present application.
2. Claims 45-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 16, 2011.
3. Claims **39-43, 48** and **52-55**, to the extent they are drawn to the elected species of schizophrenia, are under examination in the current office action.

Withdrawn Claim Rejections

4. Any objection or rejection of record pertaining to claim 49 is rendered moot on account of Applicant's cancellation of said claim.
5. The rejection of claim 40 under 35 U.S.C. 112, 4th paragraph, as being of improper dependent form, set forth at paragraph 8 of the previous office action (mailed 08/23/2011), is withdrawn in view of Applicant's amendments to the claim.

6. The rejection of claims 39-43 and 52-55 under 35 U.S.C. 102(b) as being anticipated by WO 01/52878 by Eisenbach-Schwartz et al. is withdrawn in view of Applicant's amendments to the claims. In particular, Applicant has deleted recitation of treatment of a schizophrenia related disorder, such as a brief psychotic disorder.

Maintained and New Claim Rejections, Necessitated by Amendment

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims **39-43, 48** and **52-55** are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/52878 by Eisenbach-Schwartz (of record) as evidenced by the Wikipedia entry for "Aluminum hydroxide" (Aug. 18, 2011; of record), and in view of Farber et al. (*Mol Psychiatry*, 2002; 7(1):32-43). The rejection is maintained for reasons of record for claim 48 and is further applied to claims 39-43 and 52-55, as amended.

Eisenbach-Schwartz et al. teach a method of treating injury to, or diseases of, the central nervous system comprising administering Copolymer 1 (Cop 1), a Cop 1-related peptide or polypeptide, or activated T cells that recognize an antigen of Cop 1 or a Cop1-related peptide or polypeptide (see abstract). Eisenbach-Schwartz teaches that in one embodiment, Cop 1 or a Cop 1-related peptide or polypeptide is administered in methods for protecting CNS cells from glutamate toxicity or for treating injury or disease caused or exacerbated by glutamate toxicity (see p. 24, lines 25-29). In particular, Eisenbach-Schwartz notes that in light of the findings with respect to the glutamate protective aspect of the disclosed invention, clinical conditions that may be treated in accordance with the disclosed invention include anxiety and psychosis (see p. 34, lines 5-9). Eisenbach-Schwartz further comments that protection against glutamate toxicity can also be achieved using Cop 1-related T cell treatment (see p. 34, lines 17-20). Hence, the reference teaches treating a patient having psychosis comprising administering Cop 1, a Cop 1-related peptide or polypeptide, or T cells activated by Cop

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1 or a Cop 1-related peptide or polypeptide, which is on point to the specific agents as recited in present claims 41-43.

With respect to claims 40 and 52-55, Eisenbach-Schwartz discloses that pharmaceutical compositions comprising Cop 1 or Cop 1-related peptide or polypeptide may optionally be administered with an adjuvant, such as alum, in the usual manner for immunization (see p. 40, lines 1-5). Note that the term alum, particularly when used as an adjuvant in vaccine preparations, is a generic name for aluminum hydroxide, which is safe for human clinical use. (See 1st paragraph of page 4 of Wikipedia entry for "Aluminum hydroxide", which notes that "[a]luminum hydroxide is often mis-called "alum" even by researchers".) Because Eisenbach-Schwartz teaches that the use of an adjuvant is optional, this would account for administration of Cop 1 without an adjuvant, as in claim 53.

The difference, therefore, between the teachings of Eisenbach-Schwartz and the presently claimed invention is that the prior art reference does not teach that the psychosis is schizophrenia.

Farber et al. teach that NMDA receptor hypofunction (NRHypo)-induced neurotoxicity may underlie neurodegeneration and psychosis in diseases such as Alzheimer's disease and schizophrenia (see abstract). The NMDA receptor is, of course, a receptor for glutamate and thus is responsible for excitatory glutamatergic signaling in the CNS.

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to have modified the teachings of Eisenbach-Schwartz to treat

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patients having schizophrenia by administering Cop 1. The skilled artisan would have been aware of the teachings of Eisenbach-Schwartz, for example, which state that psychosis can be treated by using Cop 1 because of the neuroprotective effects of Cop 1 against glutamate toxicity. In view of the teachings of Farber et al., the ordinary skilled artisan would have also recognized that schizophrenia, which is a psychiatric disorder comprising psychosis as a predominant component of the disease, is associated with glutamate receptor dysregulation, including neurotoxicity resulting therefrom (i.e., glutamate-related neurotoxicity). Therefore, it would have been obvious to use an agent (Cop 1) taught be useful in abrogating glutamate toxicity in psychosis for the treatment of such pathology in schizophrenia. This is because the skilled artisan has good reason to pursue the known options within his or her technical grasp to yield predictable results. Particularly in view of the fact that psychosis is a major component of schizophrenia, such would amount to the simple substitution of one known element (i.e., treatment of psychosis) for another (i.e., treatment of schizophrenia, which is characterized by psychosis) to obtain predictable results.

Response to Arguments

9. In the response filed November 23, 2011, Applicants note that psychosis is part of a number of psychiatric disorders, including bipolar disorder, delusional disorder, depression with psychotic features, personality disorders, schizoaffective disorder and schizophrenia, and have provided medical encyclopedia definitions for “psychosis” and “schizophrenia” as evidence (see under arguments for 102(b) rejection). Therefore, Applicants allege, the examiner is incorrect in interpreting the term “psychosis” as

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meaning "schizophrenia". Furthermore, Applicants argue that Farber et al. does not teach that schizophrenia is associated with glutamate receptor-induced neurodegeneration or neurotoxicity, but instead teaches that "NMDA antagonists have significant side effects" and can "trigger psychosis" in adult humans. According to Applicants, therefore, psychosis is triggered by the very agents used to treat neurodegeneration caused by glutamate toxicity, not by the glutamate toxicity. Applicants thus argue that the skilled artisan would have no reason to believe that schizophrenia is associated with glutamate receptor-induced neurodegeneration, and would not have motivation to combine the teachings.

10. Applicants' arguments have been fully considered but they are not persuasive. While psychosis is a general term used to describe a loss of contact with reality, it clearly is part of the symptomology encompassed by schizophrenia (as well as bipolar disorder and depression, which are also recited in claim 39). Thus, the skilled artisan would have recognized that at least the psychosis aspect of schizophrenia would be amenable to treatment according to the disclosure of Eisenbach-Schwartz. Note that there is no limiting definition for "treatment" in the present specification. Thus, the broadest reasonable interpretation of "treatment" in the claims would include improving or ameliorating any aspect of a psychiatric disorder, such as by reducing or preventing the occurrence, severity or extent of symptoms associated with the disorder. Treatment of psychosis in schizophrenia would therefore be encompassed by the presently claimed invention.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, the examiner has presented evidence to establish that schizophrenia is associated with glutamate-receptor mediated neurotoxicity, and that the use of Cop 1 or Cop 1-activated T cells, etc. can be used therapeutically in methods of protecting CNS cells from glutamate-related toxicity or for treating disease caused by or associated with glutamate toxicity.

Applicants have misconstrued the teachings of Farber et al. In contrast to Applicants' arguments, one of ordinary skill in the art would not have been dissuaded by the teachings of Farber stating that "NMDA antagonists have significant side effects" and can "trigger psychosis" in adult humans. These teachings are not inconsistent with the basic hypothesis that schizophrenia has, as its underlying pathology, dysfunction of glutamate receptors and glutamate neurotransmission. For example, Konradi & Heckers (*Pharmacol. Ther.* 2003 Feb; 97:153-179) note at p. 163 that:

...a *decrease* in the activity of NMDA receptors, as achieved with NMDA antagonists and as suspected in schizophrenia, also causes excitotoxicity. [...]
This paradoxical phenomenon is explained by a reduced activity of γ -

aminobutyric acid (GABA)ergic neurons under the control of hypoactive NMDA receptors. (Fig. 6) [...] The decreased stimulation of NMDA receptors on δ [sic] -aminobutyric acid (GABA)ergic neurons leads to a disinhibition of postsynaptic glutamate neurons, excessive glutamate release, and neurotoxicity. (Emphasis in original)

Konradi & Heckers at p. 166, section 2.3.3 further state that while neurotoxicity may not *cause* schizophrenia, "excitotoxic neurodegeneration may contribute to the *course* of the disease" (emphasis in original). Thus, the examiner was correct in stating that the teachings of Farber et al. indicate that schizophrenia is associated with glutamate-related neurotoxicity, and that based upon these teachings the skilled artisan would have been motivated to apply the therapeutic method taught by Eisenbach-Schwartz to the treatment of schizophrenia. Note that the Konradi & Heckers reference is presented merely as evidence in rebuttal of Applicants' arguments, and does not in fact change the basis of the present rejection. Accordingly, the rejection of claims 39-43, 48 and 52-55 is maintained.

11. Claims **39-43, 48** and **52-55** stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wank (*Med Hypotheses*, 2002; 59(2):154-158) in view of Ziemssen et al. (*Brain*, 2002 Nov; 125:2381-2391) and WO 01/52878 by Eisenbach-Schwartz et al. (published Jul. 26, 2001) as evidenced by the Wikipedia entry for "Aluminum hydroxide", downloaded Aug. 18, 2011. The rejection is maintained for reasons of record and as discussed below.

Response to Arguments

12. In the response filed November 23, 2011, Applicants assert the following arguments, each of which will be addressed in turn:

A. One of ordinary skill in the art would be skeptical of the Wank reference in that only a single case of treatment of a patient with schizophrenia was reported, and that the adoptive immunotherapy approach was only an “adjuvant therapy” that was used in conjunction with additional medications in the patient.

B. Wank's activated T-cells are activated by CD3 in a general manner, not against a specific antigen, and therefore are incapable of homing to specific sites in the CNS as the Cop 1 stimulated T cells of the present invention do. Applicants argue that Wank does not teach that the activated T cell can home to the CNS, and even if they did, Applicants allege that the T cells would not be neuroprotective because they would not cross-react with local antigens.

C. Eisenbach-Schwartz does not teach that the CNS damaged in a brain of a patient with schizophrenia, or with psychosis, expresses antigens that cross-react with Cop-1.

D. With respect to the Ziemssen reference, which teaches that glatiramer acetate (Cop-1) induces T cells to produce BDNF, Applicants point to their specification which indicates that it was not clear whether BDNF is beneficial in treating schizophrenia, so there would be no motivation to cause T cells to accumulate at the site of injury in the schizophrenic brain and produce BDNF there. Furthermore, Applicants note that the production of neurotrophic factors by Cop-1-activated T cells requires a local signal from resident antigen-present cells; none of the Ziemssen, Eisenbach-Schwartz, or Wank

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references teach whether such a local signal is transduced to the T cells in schizophrenia lesions. Thus, Applicants assert, it would be unpredictable whether Cop-1 activated T cells would produce BDNF at the schizophrenia lesions.

E. Ziemssen et al. do not teach whether trkB receptors (the receptor for BDNF) are expressed in schizophrenia lesions in the brain, and neither do Eisenbach-Schwartz nor Wank. Applicants argue that the lack of information regarding the expression of trkB in schizophrenia lesions would make the beneficial effects of GA-activated T cells unpredictable.

F. Thus, the skilled artisan would not have had a reasonable expectation of success in trying to treat schizophrenia by administering Cop-1 or Cop-1 activated T cells.

13. Applicants' arguments have been fully considered but they are not persuasive.

With respect to point A, it is noted that Wank's teachings are still on point to the present invention in that Wank clearly teaches that adoptive immunotherapy (i.e., the activation of T lymphocytes *ex vivo* and reintroduction to a patient) may be used to treat schizophrenia. Wank demonstrates that the proposed therapeutic method was beneficial in three case studies of patients having bipolar disorder, autism, or schizophrenia. Based upon these positive results, one of skill in the art would have had motivation to use an adoptive immunotherapeutic approach to the treatment of schizophrenia.

With respect to points B, C, E, and portions of D above, Applicants are essentially indicating that activated T cells must home to antigens that cross-react with

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Cop-1 and are expressed by schizophrenia lesions, and that schizophrenia lesions must express trkB receptors in order for the method to be therapeutically beneficial. However, the claims do not recite that Cop-1 activated T cells must home to schizophrenia lesions (or any CNS damage for that matter), or that the damaged CNS tissues must express particular antigens and/or receptors. Applicants are reminded that arguments that rely on particular distinguishing features are not persuasive when those features are not recited in the claims. The claims must be interpreted as broadly as their terms reasonably allow. See *Ex parte Oetiker*, 23 USPQ2d 1641 (BPAI, 1992). In the instant case, all the claims recite is a method of treating schizophrenia, comprising administering to an individual in need of such treatment an effective amount of Cop-1, a Cop-1 related peptide or polypeptide, or T cells activated with any of these. There is nothing in the claims that recites that the activated T cells must home to a specific site, or that the damaged area must express trkB and/or an antigen that cross-reacts with Cop-1. And even if the claims did recite such features, the claimed method would still be obvious because over the combined prior art teachings because such features would necessarily be present in either the Cop-1 activated T cells or the "damaged" CNS tissue. As evidence that such would necessarily occur, the prior art teaches that GA-specific T cells adoptively transferred to normal (i.e., non-diseased or non-brain-damaged) mice were found to localize to the brain and produce BDNF (see Aharoni et al. *Proc Natl Acad Sci USA*, 2003 Nov; 100(24):14157-14162). Hence, if GA-specific T cells are capable of homing to the CNS and producing BDNF in a non-brain-damaged or -diseased subject (as well as in subjects having damage to the CNS as in the EAE

model of the Aharoni publication), then it reasonable to predict that these activated T cells would similarly home to sites of CNS damage in the schizophrenic brain.

Moreover, in response to applicants' arguments against the references individually, such as in points B-E above, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Wank clearly teaches and suggests that adoptive immunotherapy using *ex vivo* activated T cells is beneficial for the treatment of schizophrenia, and also indicates that BDNF may play a key role in schizophrenia. Ziemssen et al. teach that Cop-1 activated T cells produce BDNF, and Eisenbach-Schwartz teaches that Cop-1 or Cop-1 activated T cells can be used to treat psychosis. Because psychosis is a predominant element of schizophrenia, and because the broadest reasonable interpretation of the claims would include treatment of any aspect of schizophrenia, such as psychotic symptoms, then it would have been obvious to use an adoptive immunotherapeutic approach for the treatment of schizophrenia, such as by administering Cop-1 activated T cells or by administering Cop-1 itself.

With respect to F, Applicants' apprehension about achieving success in trying to treat schizophrenia by administering Cop-1 or Cop-1 activated T cells is not persuasive as obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. See, e.g., *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Regardless,

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the skilled artisan would have had a reasonable expectation of success based upon the teachings of Wank, which demonstrate beneficial effects of an adoptive immunotherapeutic approach given to patients having schizophrenia, bipolar disorder or autism. Accordingly, the combined teachings of the above references render obvious the presently recited invention of claims 39-43, 48 and 52-55.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

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double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims **39-42** and **52-55** stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 6, 9, 10 and 15 of copending Application No. 12/437,167.

Response to Arguments

16. In the response filed November 23, 2011, Applicants request that this rejection be held in abeyance until such time as allowable subject matter is identified.

17. Applicants' request is acceptable. The provisional rejection is maintained until such time as allowable subject matter is identified.

18. Claims **39-43**, **52** and **53** stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 31 and 33 of U.S. Patent No. 6,844,314.

19. The examiner notes that Applicant did not address this rejection in either of the responses filed November 23, 2011 or November 28, 2011.

20. Accordingly, the present rejection is maintained for reasons of record.

Conclusion

21. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is (571)272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard
Art Unit 1649

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646